REMARKS

Review and reconsideration on the merits are requested.

Request for Suspension of Action

Applicants have requested Suspension of Action for three months with the expectation of filing a DECLARATION UNDER C.F.R. 1.132 which is currently being worked on.

DETAILED ACTION

Even though Applicants have amended the claims, they treat the Action of March 10, 2008 (Final Rejection) as though it were to be posed against the present claims.

Art Rejections in the Parent

Claims 12-13 were rejected under 35 U.S.C. § 102(b) as anticipated in Ohnota et al, (Ohnota) (of record).

Claims 13-14 and 24-36 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ohnota.

These rejections are respectfully traversed.

The Examiners' position is set forth in the Action and will not be repeated here except as necessary to an understanding of Applicants' traversal which is now presented.

Claim Limitation

Applicant's limit the claims to a human patient. It is believed this responds directly to the Examiner's position at page 3 of the Action 03/10/2008 (hereafter the Action) where the Examiner states:

"Applicant claims a "patient" but does not specify that it cannot be a rat or dog (such as those tested in Ohnota et al.). Since dogs get diabetes, it is a reasonable interpretation of "patient".

In light of this amendment, Applicant's directly address the Examiner position at page 3 of the Action that Ohnota teaches a method of administering 5 to 45 mg of mitiglinide calcium hydrate to a type II diabetic patient, and that would inherently lower *postprandial and fasting blood glucose levels* such as claimed and claims 12 and 13 are anticipated by Ohnota et al.

Ohnota's teaching is completely different from the present invention. In the experiments disclosed in Ohnota, KAD-1229 was administered in a range of 0.3 to 3.0 mg/kg or 0.1 to 3.0 mg/kg *to fasted normal rats or dogs*, respectively, and it was merely confirmed that KAD-1229 possessed a hypoglycemic effect (see Figs 2 and 3: Time courses of plasma glucose levels after the drug administration). One of ordinary skill in the art would clearly understand that these experiments were not conducted to examine the effect on postprandial or fasting blood glucose levels and thus the dosages disclosed by Ohnota do not teach or suggest the effective dosage to control postprandial and fasting blood glucose levels without causing prolonged hypoglycemia in human diabetic patents (hereafter human is often omitted in the discussion). Therefore, claims 12-13 are not anticipated or suggested by Ohnota.

Glycemic Control

The term "glycemic control" per the present invention means not merely lowering blood glucose levels but controlling the circadian blood glucose change of a diabetic patient so as to be close to that of a healthy subject, in particular, lowering postprandial blood glucose levels and fasting blood glucose levels without causing prolonged hypoglycemia.

As described in the present specification at page 3, lines 8-11, HbA_{1C} and fasting blood glucose level have been considered as indexes for the diagnosis and treatment of diabetes and are intimately related to the prevention of diabetic microvascular complications including what are considered the three major diabetic complications nephropathy, retinopathy and neuropathy. See page 2, lines 16/17 and page 3, lines 8-11 of the specification.

Postprandial Blood Glucose Levels

It has recently been considered that a precipitous postprandial increases in blood glucose, called a "glucose spike", causes oxidative stress, followed by damage to large vessels, reaching the stage of macrovascular diseases. For this reason, postprandial blood glucose levels have attracted attention as an important factor in the treatment of diabetic macrovascular complications. The term "glucose spike" is a term commonly used by those skilled in the art to express intermittent postprandial blood glucose elevation. However, one can use another expression such as "intermittent postprandial blood glucose elevation" instead of "glucose spike".

Since arteriosclerotic diseases (macrovascular diseases) are considered very severe diabetic complications as compared to microvascular diseases, postprandial blood glucose level is more important than HbA_{1C} or fasting blood glucose.

As a consequence, in practicing glycemic control for the treatment of diabetes, it is extremely important to improve both fasting blood glucose levels as a baseline and glucose

spike, the rapid postprandial change of blood glucose levels, and, at the same time, not to cause prolonged hypoglycemia.

Suppressing Postprandial Hyperglycemia Without Causing Hypoglycemia Between Meals

In order to suppress postprandial hyperglycemia without causing hypoglycemia between meals, a rapid- and short-acting drug which greatly lowers postprandial blood glucose is considered in the art to be desirable. For example, sulfonylurea antidiabetics strongly lower postprandial hyperglycemia but sometimes cause hypoglycemia between meals. On the other hand, a short-acting drug which only lowers postprandial blood glucose is unlikely to lower fasting blood glucose. This is seen with α-glucosidase inhibitors such as voglibose. Thus, the art considers it very difficult to achieve both incompatible effects in view of the results with sulfonylurea antidiabetics and α-glucosidase inhibitors.

Insulin is a kind of hormone and plays a role in lowering blood glucose levels. Mitiglinide calcium salt hydrate of the present invention is a rapid- and short-acting insulin secretagogue (secretion enhancer). In normal subjects, when the blood glucose level increases after starting a meal, insulin is promptly secreted and, as a result, a postprandial large increase of blood glucose can be suppressed. On the other hand, in diabetic patients, even when blood glucose levels increase after starting a meal, insulin secretion does not promptly occur, that is, there is delayed insulin secretion, and, therefore, the postprandial blood glucose level becomes higher than normal. In addition, the peak of postprandial high blood glucose is earlier than 2

hours after a meal in both normal subjects and diabetic patients. Applicant's submitted a reference which supported these remarks with their response of January 10, 2008. See Fig. 1 at page 28. The upper line of the figures are blood glucose levels after a meal in NGT (normal glucose tolerance) to DM (diabetes mellitus), and the lower line of the figures are insulin levels. It can be seen that in the DM group, insulin secretion occurs later than in the NGT group and the peaks of blood glucose level are earlier than 120 minutes in all groups. An English translation in part was filed with the IDS of February 14, 2008.

Applicants respectfully submit that considering the above knowledge which would be in the hands of one of ordinary skill in the art, it is quite surprising that, in accordance with the method of the present invention, both fasting and postprandial hypoglycemia can be inhibited without causing prolonged hypoglycemia following a specific dose regimen and a specific dose timing. See the later discussion of the clinical study on type II diabetic patients as described in the present specification which led to the method of the present invention.

Another aspect which led to the present invention is also quite important. Although blood glucose levels 2 hours after glycemic loading have generally been used as an index of postprandial hyperglycemia, it was recently reported that the peak of postprandial hyperglycemia is earlier than 2 hours, that is, it is 1 hour after a meal, with delayed insulin secretion in diabetic patients. As a consequence, by stimulating earlier stage postprandial insulin secretion, changes in blood glucose levels can be brought closer to those of a normal subject.

Clinical Study

As briefly discussed above, α-glucosidase inhibitors are drugs which can inhibit early-stage postprandial hyperglycemia. Surprisingly, based on the method of the present invention, mitiglinide exerted a more excellent effect in 1 hour and 2 hour values of postprandial plasma glucose as well as fasting plasma glucose as compared with voglibose, a known α-glucosidase inhibitor. This was confirmed by the clinical studies described in the present application (Example 3, Tables 3 and 4). Applicants submit that this is another important factor in establishing the novel and unobvious nature of the claims of the present application as now amended.

In more detail on voglibose, one of the α-glucosidase inhibitors, this is a known drug which can inhibit early-stage postprandial hyperglycemia. As shown in Example 3 herein, including Tables 3 and 5, mitiglinide calcium salt hydrate (a present invention compound) exerted a substantially greater potent activity than voglibose (positive control group) in fasting plasma glucose (Table 3) as well as 1 hour and 2 hour values of postprandial plasma glucose (Table 4) without a greater frequency of hypoglycemic symptoms as compared to voglibose (Table 5).

Ohnota

Applicants would now like to turn to the prior art relied upon by the Examiner, namely Ohnota.

Ohnota teaches KAD-1229 (mitiglinide calcium hydrate) is a promising antidiabetic agent because its rapid and short action would produce stricter and safer control of plasma

glucose levels in NIDDM patients. However, since Ohnota shows only data of plasma glucose level in *fasted normal rats or dogs,* even if a dosage in the range of 0.3 to 3.0 mg/kg is described, Ohnota does not teach or suggest anything to one of ordinary skill in a suitable dosage regimen and a suitable dosage timing regimen in order to achieve the above-mentioned unexpected effect such as controlling circadian blood glucose changes in a human diabetic patient (type II diabetes) so as to make the same close to that of a healthy human subject.

Claim 24

At page 6 of the Action, the Examiner states:

"[A] lthough Ohnota et al. does not disclose such specifics, it would be obvious to one of skill in the art at the time of the invention that a patient with those levels would also be in need of lowering postprandial blood glucose levels and thus the method of Ohnota et al. would be expected to help the patient of claim 24, and claim 24 is unpatentable over Ohnota et al."

The Examiner has offered nothing to support this conclusion, and Applicants respectfully submit that, without such support, claim 24 stands allowable.

Claims 33-36

At page 7 of the Action, the Examiner states:

"Since it is common to eat three meals per day, and thus taking something before each meal of the day would have been obvious to one of ordinary skill in the art. Continuing the therapy for four weeks or more would also be obvious to one of ordinary skill in the art at the time of the invention, as most diabetic blood glucose treatments are administered continuously as maintenance drugs. Thus claim 33-36 are unpatentable over Ohnota, et al."

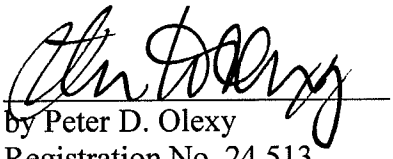
Applicants respectfully submit the Examiner to be in error in the above statement since simply because someone eats three meals a day does not lead to the conclusion that taking something before each meal of the day would have been obvious. For example, many medications are given only once a day or more than three time per day.

With respect to "continuing the therapy for four weeks or more", even assuming that the Examiner is correct in the statement that most "diabetic blood glucose treatments are administered continuously as maintenance drugs.", this does not necessarily suggest four weeks or more, i.e., this could suggest one day or more, one week or more, etc. The Examiner is respectfully to specifically consider the "four weeks or more" limitation.

Considering all of the above, allowance is requested after Suspension of Action is lifted.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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